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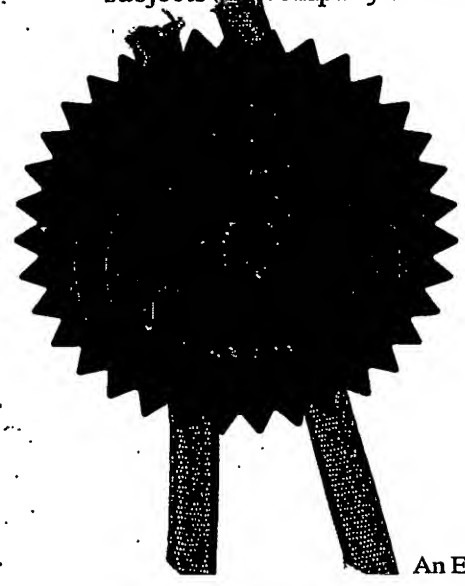

Signed R. Mahoney

Dated 23 October 2002

Patents Form 1/77

Patents Act 1977
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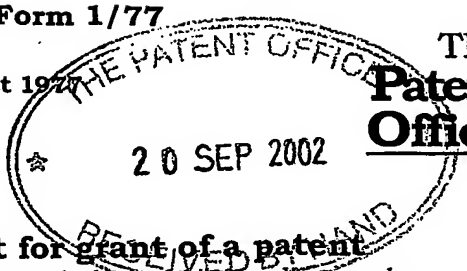

The **Patent Office**

1/77

226EP02 E750022-3 D00524
P01/7700 0.00-0221953.3

Request for grant of a patent

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1.	Your reference	**4-32651P1/NFI 8026**
2.	Patent application number *(The Patent Office will fill in this part)*	0221953.3 — 20 SEP 2002
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	**NOVARTIS AG** **LICHTSTRASSE 35** **4056 BASEL** **SWITZERLAND**
	Patent ADP number *(if you know it)*	7125487005
	If the applicant is a corporate body, give the country/state of its incorporation	**SWITZERLAND**
4.	Title of invention	**Organic compounds**
5.	Name of your agent *(If you have one)*	
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	**B.A. YORKE & CO.** **CHARTERED PATENT AGENTS** **COOMB HOUSE, 7 ST. JOHN'S ROAD** **ISLEWORTH** **MIDDLESEX TW7 6NH**
	Patents ADP number *(if you know it)*	**1800001**

		Country	Priority application number *(if you know it)*	Date of filing (day/month/year)
6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number			

		Number of earlier application	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	**Yes**

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9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	13
Claim(s)	2 DML
Abstract	1
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Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	ONE
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature B.A. Yorke & Co. Date **20 September 2002**

B.A. Yorke & Co.

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. E. Cheetham
020 8560 5847

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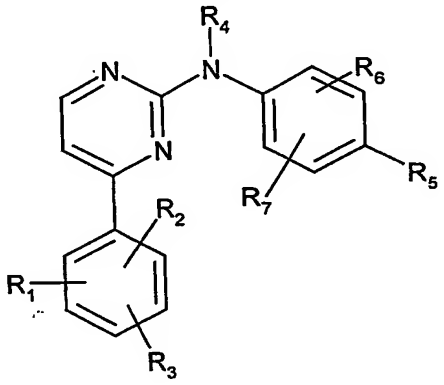
Organic compounds

The present invention relates to organic compounds having pharmaceutical e.g. IgE-synthesis inhibiting, activity.

In one aspect the present invention provides a compound of formula



I

wherein

at least one of R_1, R_2 and R_3 is halogen or haloalkyl, and the other of R_1, R_2 and/or R_3 are independently of each other hydrogen, halogen or haloalkyl,

R_5 is halogen or haloalkyl,

R_6 and R_7 independently of each other are hydrogen, halogen, or haloalkyl, and

R_4 is hydrogen, alkyl or a group of formula

$-CO-(CH_2)_n-CO-R_8$,

$-CO-(CH_2)_n-O-(CH_2)_n-CO-R_8$ or

$-CO-(CH_2)_n-O-(CH_2)_m-O-(CH_2)_n-R_{12}$, wherein

R_8 is $-OR_9$, $-NR_{10}R_{11}$, an amino acid or an ester thereof bound via the amino group,

R_9 is hydrogen or alkyl,

R_{10} and R_{11} independently of each other are H, alkyl or substituted or unsubstituted aminoalkyl;

R_{12} is hydrogen, alkyl, carboxyl or carboxylic ester,

n is 0 to 4, and m is 1 to 5.

Preferably

- the pyrimidine is substituted by phenyl in position 4 of the pyrimidine ring;
- the pyrimidine is bound to the amine in position 2 of the pyrimidine ring;
- at least one of the phenyl rings bound to the amine or to the pyrimidine is substituted;

- at least one, preferably both, of the phenyl rings bound to the amine or to the pyrimidine, respectively, is/are substituted by halogen or haloalkyl.

In another aspect the present invention provides a compound of formula I, selected from the group consisting of
N-[4-(3-Chloro-phenyl)-pyrimidin-2-yl]-N-(4-chloro-3-trifluoromethyl-phenyl)-amine,
N-[4-(3-Trifluoromethyl-phenyl)-pyrimidin-2-yl]-N-(4-fluoro-3-trifluoromethyl-phenyl)-amine,
N-[4-(3-Trifluoromethyl-phenyl)-pyrimidin-2-yl]-N-(4-chloro-3-trifluoromethyl-phenyl)-amine,
N-[4-(3-Trifluoromethyl-phenyl)-pyrimidin-2-yl]-N-(4-trifluoromethyl-phenyl)-amine, and
N-[4-(3-Chloro-phenyl)-pyrimidin-2-yl]-N-(4-trifluoromethyl-phenyl)-amine,
wherein the amine group is further substituted by R_4, wherein R_4 is as defined above.

In a further aspect the present invention provides a compound of formula I wherein one of R_1, R_2 or R_3 is chloro and the other two are H, one of R_5, R_6 or R_7 is trifluoromethyl and the other two are H, and R_4 is $-CO-(CH_2)_nCO-R_8$, wherein
R_8 is OR_9, $N(CH_3)_2$, $N(CH_3CH_2)_2$, $NH-(CH_2)_3-N(CH_3)_2$, amino acid or an ester thereof, preferably an amino acid selected from the group consisting of alanine, phenylalanine, glutamic acid and lysine, wherein the binding is effected via the α- amino group or in the case of e.g. lysine via the ε-amino group, R_9 is hydrogen or alkyl, and n is 1 to 4, preferably 2,3 or 4.

In another preferred aspect the present invention provides a compound of formula I wherein one of R_1, R_2 or R_3 is chloro and the other two are H, one of R_5, R_6 or R_7 is trifluoromethyl and the other two are hydrogen, and R_4 is $-CO-(CH_2)_nO-(CH_2)_n-CO-R_8$ wherein R_8 is OR_9, R_9 is hydrogen or alkyl, and n is 1 to 4, preferably 2, 3 or 4.

In a further preferred aspect the present invention provides a compound of formula I wherein one of R_1, R_2 or R_3 is chloro and the other two are hydrogen, one of R_5, R_6 or R_7 is trifluoromethyl and the other two are H, and R_4 is $-CO-(CH_2)_n-O-(CH_2)_m-O-(CH_2)_n-R_{12}$ wherein R_{12} is hydrogen, alkyl, carboxyl or carboxylic ester, n is 1 to 4, preferably 1 or 2, and m is 1 to 5, preferably 2 or 5.

In another aspect the present invention provides the use of an amine, which is substituted by
- phenyl-substituted pyrimidin; and
- phenyl; and

- a third substituent,

in the preparation of a medicament for the treatment of IgE-synthesis-mediated diseases.
A third substitutent e.g. includes a group R_4 as defined above.

If not otherwise defined herein alkyl includes (C_{1-6})alkyl, e.g. (C_{1-4})alkyl. Aryl includes phenyl. Halogen includes fluoro, chloro, bromo. Haloalkyl includes halo(C_{1-4})alkyl, wherein halo is one or more halogen, preferably trifluoromethyl. Cycloalkyl includes (C_{3-8})cycloalkyl, e.g. (C_{3-6})cycloalkyl. Aminoalkyl includes amino(C_{1-6})alkyl, e.g. amino(C_{1-4})alkyl, preferably disubstituted aminoalkyl, e.g. dimethyl- or diethylaminoalkyl.
Any group may be unsubstituted or substituted, e.g. substituted by groups as conventional in organic chemistry, e.g. including groups selected from halogen, haloalkyl, alkylcarbonyloxy, alkoxy, hydroxy, amino, alkylcarbonylamino, aminoalkylcarbonylamino, hydroxyalkylamino, aminoalkylamino, alkylamino, dialkylamino, heterocyclyl, alkylheterocyclyl, hydroxyalkylheterocyclyl, carboxyl, alkylcarbonyloxy, aminoalkylcarbonyloxy.

Compounds provided by the present invention are hereinafter designated as "compound(s) of the present invention". A compound of the present invention includes a compound in any form, e.g. in free form, in the form of a salt, in the form of a solvate and in the form of a salt and a solvate.

A salt of a compound of the present invention includes a pharmaceutically acceptable salt, e.g. including a metal salt or an acid addition salt. Metal salts include for example alkali or earth alkali salts; acid addition salts include salts of a compound of formula I with an acid, e.g. including inorganic and organic acids, e.g. including pharmaceutically acceptable acids, such as hydrochloric acid, sulfuric acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, tartaric acid.
A compound of the present invention in free form may be converted into a corresponding compound in the form of a salt; and vice versa. A compound of the present invention in free form or in the form of a salt and in the form of a solvate may be converted into a corresponding compound in free form or in the form of a salt in unsolvated form; and vice versa.
A compound of the present invention may exist in the form of isomers and mixtures thereof; e.g. optical isomers, diastereoisomers, cis-trans conformers. A compound of the present invention may e.g. contain asymmetric carbon atoms and may thus exist in the form of enantiomeres, diastereoisomeres and mixtures thereof, e.g. racemates. E.g. a substitutent

attached to an asymmetric carbon atom in a compound of the present invention may be in the R- or in the S-configuration, including mixtures thereof. A substituent, e.g. alkyl, in a group -O-containing substituents as a part of a compound of the present invention may be in the syn or in the anti form. The present invention includes a compound of the present invention in any isomeric form and in any isomeric mixture.

Any compound described herein, e.g. a compound of the present invention, may be prepared as appropriate, e.g. according to a method as conventional, e.g. or as described herein.

The compounds of the present invention exhibit in vivo pharmacological activity and are therefore useful as pharmaceuticals:
Immunoglobulin E (IgE) is critically involved in the pathogenesis and maintenance of allergic diseases such as atopic dermatitis, allergic asthma, allergic conjunctivitis and allergic rhinitis. To date, patients suffering from atopic dermatitis may be mainly treated with local or systemic glucocorticoids, ultraviolet light or, in severe cases, with immunosuppressants such as cyclosporin. Allergic asthma patients may be mainly treated with glucocorticoids or theophylline. Such compounds may suffer from various side effects and may not achieve the goal of reversal of disease progression in addition to alleviation of symptoms. It has been demonstrated recently that interference with IgE production or inactivation of its effector function once it has been synthesized in the body, may reduce allergic immune response and, consequently, may lead to amelioration of the disease. However, no specific inhibitor of IgE production in human B-lymphocytes is commercially available yet.
It has now been found that, the compounds of the present invention may act as specific inhibitors of IgE synthesis. Upon systemic or oral administration a compound of the present invention may suppress immunoglobulin synthesis, in particular the synthesis of immunoglobulin E in B-lymphocytes, i.e. a compound of the present invention may exhibit isotype specificity. Further it was found that a compound of the present invention may not inhibit B-cell proliferation in concentrations below the concentrations needed to block IgE synthesis.

These activities can be shown in the following assays. Temperature are in degrees Celsius and are uncorrected. The following abbreviations are used:

ELISA	enzyme-linked immunosorbent assay
FACS	fluorescence-activated cell sorting
IgE	immunoglobulin E

IL-4	interleukin-4
IL-10	interleukin-10
IMDM	Iscove's modified Dulbecco medium
SRBC	sheep red blood cells
RT	room temperature

1. Isotype specificity:

Inhibition of immunoglobulin synthesis induced in primary human B-lymphocytes stimulated by cytokines and anti-CD40 antibody

Mononuclear cells are purified from normal human spleens. The resulting cell suspension contains 50-70% B-lymphocytes as judged by CD19 expression in a FACS analysis. Using 96-well round-bottomed microtiter plates (Costar) $5x10^4$ spleenocytes are set up in a final volume of 200 µl/well in IMDM. After pre-incubation with test compound for one hour the cells are cultured to induce IgE production for 9 days at 37° in air supplied with 5 % CO_2 in the presence of 50 ng/ml of IL-4 and 500 ng/ml of anti-CD40 antibody. The culture cell supernatants are collected and quantitated for IgE by standard isotype specific sandwich ELISA. For the induction of IgG synthesis, the cells are cultured with 100ng/ml IL-10 and 500 ng/ml of anti-CD40 antibody for the same time period before IgG levels are quantitated in the cell supernatants by isotype specific ELISA.

In these tests the compounds of the present invention inhibit IgE production preferentially over IgG (IgG1).

2. B-cell proliferation

Normal human B-lymphocytes are purified from tonsils by removing contaminating T-cells with SRBC-rosetting according to M.S. Weiner et al. , Blood 42 (1973) 939. The resulting B-cells are more than 95% pure as judged by CD19 expression in a FACS analysis. Using 96-well round-bottomed microtiter plates (Costar) $1x10^5$ spleenocytes are set up in a final volume of 200 µl/well in IMDM. After pre-incubation with test compound for one hour, cell proliferation is induced with 50 ng/ml IL-4 and 500ng/ml anti-CD40 antibody. After a 4 day incubation period at 37° in air supplied with 5% CO_2, 1 µCi of tritiated thymidine is added and the cells are cultured for ca. 16 hours. The cells are collected on a nitrocellulose filter and the DNA-bound radioactivity is quantitated by liquid scintillation counting.

In these tests compounds of the present invention inhibit IL-4 and anti-CD40 antibody mediated B-cell proliferation above the concentrations needed to block IgE synthesis.

3. Determination of stability of compounds of the present invention in plasma

Heparinized blood is obtained from human volunteers and from Balb/c mice. Blood obtained is centrifuged for 4 minutes at 13,000 rpm at room temperature (RT) to obtain plasma. To aliquots of plasma (1 ml) test compounds, i.e. compounds of the present invention, are added (1 µl of 10 mM stock solutions in DMSO or water). The samples are incubated at 37°. At various time points, aliquots of 100 µl are taken from said samples. An internal standard (5 µl of a 100 µg/ml solution of an internal standard compound in methanol) is added, followed by 300 µl of methanol (or acetonitrile or acetonitrile/1 M HCl, as required). Samples are centrifuged for 5 minutes at 13,000 rpm.

For analysis, 50 µl of the supernatants obtained are injected into an HPLC system (HP1090), equipped with a Hypersil BDS C-8 column (5 µm, 250x4.6 mm) plus pre-column (10x4.6 mm). The column is eluted isocratically at 55°C and at a flow rate of 1.5 ml/min with mixtures of acetonitrile and 10 mM $(NH_4)_2SO_4$, pH 2.7; the acetonitrile content of the mixtures used is in the range of 55 - 65 % for various substances.

Analysis of specific compounds may require a different HPLC-system, e.g. column: Zorbax Extend C18 (3.5 µm, 150x4.6 mm); pre-column: Hypersil BDS, C-8 (5 µm, 10x4.6 mm); RT; acetonitrile contents of solvent: 65 %.

UV detection is carried out at 277 nm. For calibration, plasma samples are spiked with a compound of formula I wherein R_4 is hydrogen, or with a compound of formula I wherein R_4 is as defined above, but other than hydrogen; both in the range of 0.5 to 20 µM, and internal standard. Absolute concentrations are calculated using these calibration sets.

In these determination tests it was found that a compound of formula I wherein R_4 is as defined above, but other than hydrogen has a lower stability in plasma than a compound of formula I wherein R_4 is hydrogen. From that it may be assumed that compounds of formula I wherein R_4 is as defined above, but other than hydrogen, may be regarded as prodrugs of compounds of formula I, wherein R_4 is hydrogen. Compounds of formula I, wherein R_4 is hydrogen, on the other hand, may establish a highly active principle, e.g. may establish the basic structure for the surprising activity of a compound of the present invention which was found in vitro and in vivo. Compounds of formula I, wherein R_4 is hydrogen may thus be regarded as those compounds having the regular drug structure.

Compounds of the present invention show a good solubility and good plasma levels after e.g. oral administration.

The compounds of the present invention are therefore indicated for use as inhibitors of immunoglobulin synthesis, especially inhibitors of IgE synthesis, and are useful in the treatment of IgE-mediated diseases, particularly IgE-mediated allergic diseases, e.g. of

diseases mediated by IgE expression, such as atopic dermatitis, particularly in children, urticaria, particularly acute urticaria, allergic asthma, allergic rhinitis, food allergies, allergic conjunctivitis, hayfever, bullous pemphigoid, industrial sensitization and chronic rejection of transplants.

For the above uses the dosage to be used will vary, of course, depending e.g. on the particular compound employed, the mode of administration and the treatment desired. However, in general satisfactory results may be obtained when the compounds are administered at a daily dosage of from about 1 mg/kg to about 30 mg/kg animal body weight, suitably given in divided doses two to four times daily. For most larger mammals the total daily dosage is from about 70 mg to about 2000 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form. Unit dosage forms comprise, for example, from about 17.5 mg to about 1000 mg of compound in admixture with at least one solid or liquid pharmaceutically acceptable carrier or diluent.

A compound of the present invention may be administered in similar manner to known standards such as glucocorticoids and antihistaminics for use in such indications. It may be admixed with conventional therapeutically acceptable carriers and diluents and, optionally, further excipients, and administered e.g. orally in such forms, e.g. in the form of tablets, capsules; or, alternatively, it may be administered topically, e.g. in conventional forms, such as aerosols, ointments or creams; parenterally or intravenously. The concentration of the substance will, of course vary, e.g. depending on the compound administered, the treatment desired and the nature of the form. In general, however, satisfactory results may be obtained in topical application forms at concentrations of from about 0.05 % to about 5 %, particularly from about 0.1 % to about 1 % by weight.

In another aspect the present invention provides the use of a compound of the present invention in the preparation of a medicament for the therapy of IgE-mediated diseases, e.g. of diseases mediated by IgE expression.

Pharmaceutical compositions for use in the therapy of IgE-mediated diseases may be prepared by mixing a compound of the present invention together with at least one pharmaceutically acceptable carrier or diluent.

In another aspect the present invention provides a method of treatment of IgE-mediated diseases which comprises administering a therapeutically effective amount of a compound

of the present invention, e.g. in the form of a pharmaceutical composition, to a subject in need of such treatment.

A compound of the present invention may be well tolerated, as may be determined according to a method as conventional. A compound of the present invention may possess beneficial pharmacogalenical properties, such as good solubility in various solvents.

In another aspect the present invention provides a compound of the present invention for use as a pharmaceutical, preferably in indications of IgE mediated diseases.

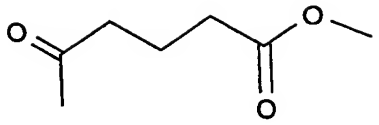
The compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt, e.g. an acid addition salt or metal salt; or in free form; optionally in the form of a solvate. The compounds of the present invention in the form of a salt exhibit the same order of activity as the compounds of the present invention in free form; optionally in the form of a solvate.

In another aspect the present invention provides a pharmaceutical composition comprising a compound of the present invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured according to a method as conventional.

In the following examples which illustrate the invention references to temperature are in degrees Celsius and are uncorrected. In the ^{1}H-NMR chemical shifts are given in delta units; J values in Hz. The following abbreviations are used:

m.p. melting point
RT room temperature
br. broad

Example 1

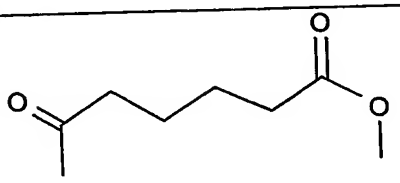
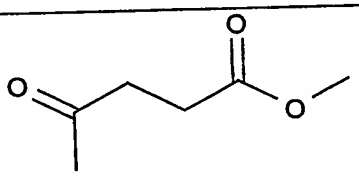
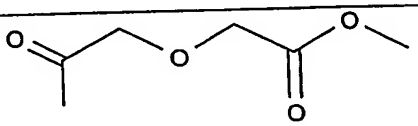
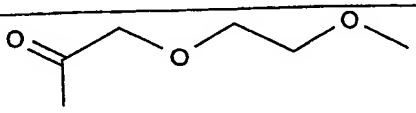
R_4 is 

A mixture of 1 g of N-[4-(3-chloro-phenyl)-pyrimidin-2-yl]-N-(4-trifluoromethyl-phenyl)-amine, 1.98 ml of glutaric acid monomethyl ester chloride, 1.1 ml pyridine and 10 mg of dimethylaminopyridine in 25 ml of toluene is heated. The mixture is diluted with ethyl acetate, washed with cold 0.01 N aq HCl, aq. bicarbonate and brine. The organic phase is dried, solvent evaporated and the product is obtained.

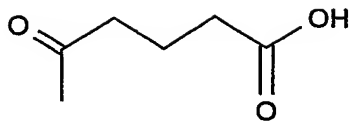
(d_6-DMSO, 500 MHz, rt): 8.83 (d, J = 5.2, 1H); 8.12 - 8.10 (m, 1H); 8.10 - 8.07 (m, 1H); 8.02 (d, J = 5.2, 1H); 7.79 (d, J = 8.5, 2H) 7.65 - 7.62 (m, 1H); 7.57 (t, J = 7.8, 1H); 7.47 (d, J = 8.2, 2H); 3.53 (s, 3H); 2.84 (t, J = 7.3, 2H); 2.38 (t, J = 7.5, 2H); 1.89 (quintett, J = 7.3, 2H)

Analogously as described in example 1 but using appropriate starting material, compounds of formula I, wherein R_4 is as described in TABLE 1 below, having ^{1}H-NMR or m.p. as defined in TABLE 1 are obtained:

TABLE 1

Example	R_4	m.p./^{1}H-NMR (d_6-DMSO, 500 MHz, RT, unless given otherwisse)
2		8.83 (d, J = 5.2, 1H); 8.12 - 8.11 (m, 1H); 8.10 - 8.08 (m, 1H); 8.02 (d, J = 5.2, 1H); 7.78 (d, J = 8.5, 2H); 7.65 - 7.62 (m, 1H); 7.58 (t, J = 7.9, 1H); 7.45 (d, J = 8.3, 2H); 3.54 (s, 3H); 2.79 (t, J = 7.5, 2H); 2.29 (m, 2H); 1.68 - 1.62 (m, 2H); 1.52 - 1.48 (m, 2H)
3		(400 MHz): 8.84 (d, J = 5.3, 1H); 8.13 - 8.09 (m, 2H); 8.02 (d, J = 5.3, 1H); 7.80 (d, J = 8.4, 2H); 7.64 - 7.62 (m, 1H); 7.57 (t, J = 7.8, 1H); 7.46 (d, J = 8.2, 2H); 3.59 (s, 3H); 3.12 - 3.08 (m, 2H); 2.68 - 2.65 (m, 2H)
4		8.77 (d, J = 5.5, 1H); 8.08 - 8.07 (m, 2H); 7.96 (d, J = 5.2, 1H); 7.83 (d, J = 8.5, 2H); 7.65 - 7.62 (m, 1H); 7.57 (t, J = 8.1, 1H); 7.51 (d, J = 8.2, 2H); 4.90 (s, 2H); 4.22 (s, 2H); 3.61 (s, 3H)
5		8.79 (d, J = 5.5, 1H); 8.11 - 8.10 (m, 1H); 8.09 - 8.08 (m, 1H); 7.98 (d, J = 5.2, 1H); 7.81 (d, J = 8.2, 2H); 7.65 - 7.62 (m, 1H); 7.58 (t, J = 8.1, 1H); 7.47 (d, J = 8.2, 2H); 4.72 (s, 2H), 3.56 - 3.54 (m, 2H); 3.34 - 3.32 (m, 2H); 3.14 (s, 3H)

Example 6

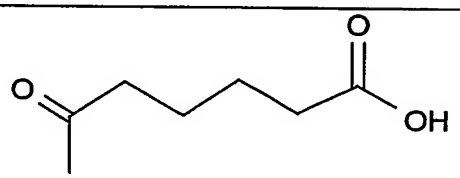
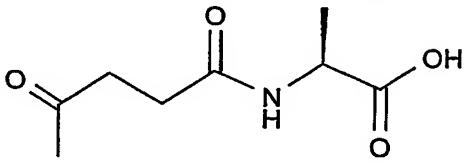
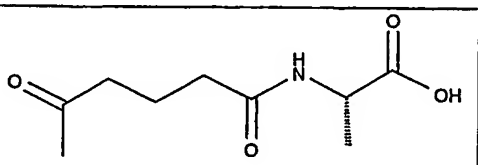
R_4 is 

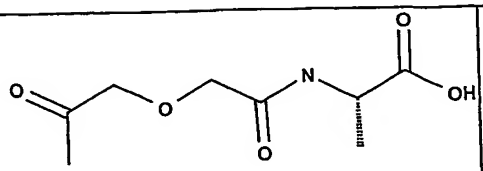
0.01 N aq. NaOH is added dropwise to a solution of 4.5 g N-[4-(3-chloro-phenyl)-pyrimidin-2-yl]-N-(4-trifluoromethyl-phenyl)-amine in a mixture of tetrahydrofuran and water. A precipitate formed is filtered off and solvent is evaporated. A mixture remaining is filtered and a filtrate obtained is acidified to pH 2 with 0.1 N HCl and extracted with ethylacetate. The organic phase is washed and dried and solvent is stripped off to give a solid. Crystallisation from a mixture dichloromethane and pentane results in the product (m.p.: 138.6 °C).

(d_6-DMSO, 500 MHz, rt): 12.01 (br, 1H); 8.83 (d, J = 5.2, 1H); 8.10 (m, 1H); 8.09 - 8.07 (m, 1H); 8.01 (d, J = 5.4, 1H); 7.78 (d, J = 8.7, 2H); 7.63 - 7.61 (m, 1H); 7.56 (t, J = 7.8, 1H); 7.47 (d, J = 8.7, 2H); 2.84 (t, J = 7.5, 2H); 2.29 (t, J = 7.4, 2H); 1.87 (quintett, J = 7.3, 2H)

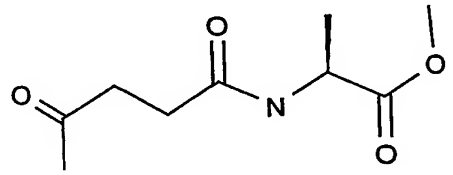
Analogously as described in example 6 but using appropriate starting material, compounds of formula I, wherein R_4 is as described in TABLE 2 below, having ^{1}H-NMR or m.p. as defined in TABLE 2 are obtained:

TABLE 2

Example	R_4	m.p./^{1}H-NMR (d_6-DMSO, 500 MHz, RT, unless given otherwisse)
7		11.98 (br, 1H); 8.83 (d, J = 5.3, 1H); 8.12 - 8.11 (m, 1H); 8.10 - 8.08 (m, 1H); 8.01 (d, J = 5.3, 1H); 7.78 (d, J = 8.3, 2H); 7.65 - 7.62 (m, 1H); 7.57 (t, J = 7.8, 1H); 7.45 (d, J = 8.3, 2H); 2.79 (t, J = 7.5, 2H); 2.19 (t, J = 7.3, 2H); 1.69 - 1.63 (m, 2H); 1.56 - 1.50 (m, 2H)
8		8.82 (d, J = 5.5, 1H); 8.15 (d, J = 7.3, 1H); 8.12 - 8.08 (m, 2H); 8.00 (d, J = 5.2, 1H); 7.78 (d, J = 8.2, 2H); 7.65 - 7.62 (m, 1H); 7.57 (t, J = 7.8, 1H); 7.46 (d, J = 8.2, 2H); 4.16 (quintett, J = 7.2, 1H); 3.05 - 2.95 (m, 2H); 2.58 - 2.52 (m, 2H); 1.22 (d, J = 7.3, 3H)
9		12.40 (br., 1H); 8.83 (d, J = 5.5, 1H); 8.11 - 8.08 (m, 2H); 8.05 (d, J = 7.3, 1H); 8.02 (d, J = 5.5, 1H); 7.78 (d, J = 8.5, 2H); 7.64 - 7,62 (m, 1H); 7.57 (t, J = 7.8, 1H); 7.47 (d, J = 8.2, 2H); 4.16 - 4.09 (m, 1H); 2.80 - 2.76 (m, 2H); 2.16 (t, J = 7.3, 2H); 1.89 - 1.81 (m, 2H); 1.17 (d, J = 7.3, 3H)

10		8.78 (d, J = 5.2, 1H); 8.09 - 8.06 (m, 2H); 7.97 (d, J = 5.2, 1H); 7.95 (d, J = 7.5, 1H); 7.83 (d, J = 8.5, 2H); 7.64 - 7.62 (m, 1H); 7.57 (t, J = 7.8, 1H); 7.52 (d, J = 8.5, 2H); 4.90 (s, 2H); 4.26 - 4.18 (m, 1H); 4.01 (s, 2H); 1.24 (d, J = 7.0, 3H)

Example 11

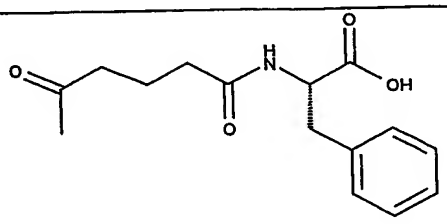
R_4 is 

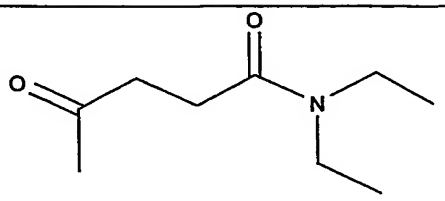
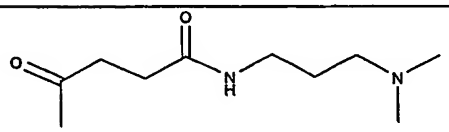
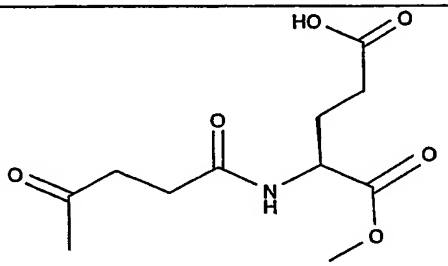
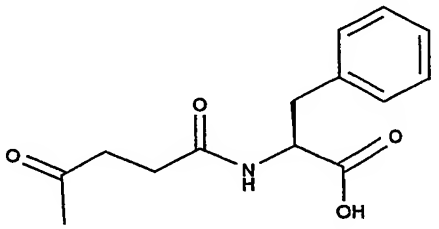
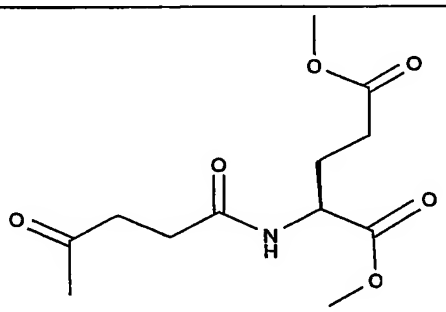
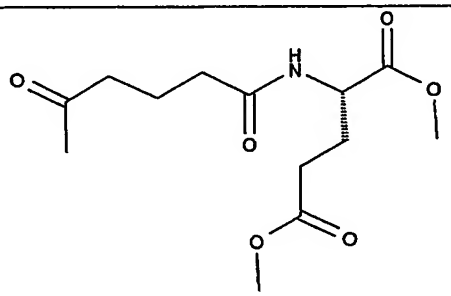
1.97 ml of diisopropylethyl amine is added dropwise to a mixture of 2 g of N-[4-(3-chloro-phenyl)-pyrimidin-2-yl]-N-(4-trifluoromethyl-phenyl)-amine, 1.21 ml of succinyl chloride and 10 mg of dimethylaminopyridine in dichloromethane. The mixture is stirred at RT, cooled and 2 g of L-alanine methyl ester hydrochloride is added. 3.4 ml of diisopropyl ethylamine is added dropwise to the mixture and stirred further. The mixture is diluted with ethylacetate, washed and dried. Solvent is evaporated and the product is obtained after crystallisation (m.p. 170.9 °C).

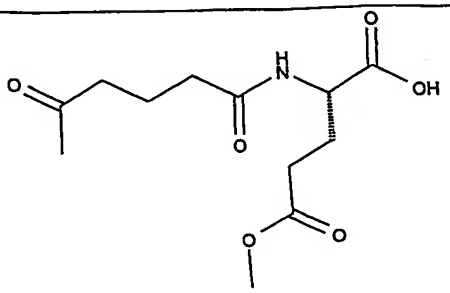
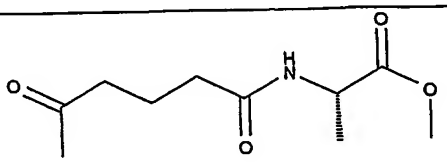
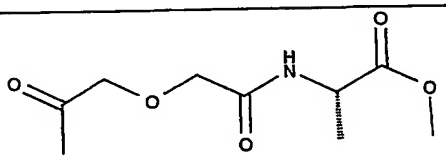
(d_6-DMSO, 500 MHz, rt): 8.83 (d, J = 5.3, 1H); 8.31 (d, J = 7.0, 1H); 8.12 - 8.08 (m, 2H); 8.01 (d, J = 5.3, 1H); 7.79 (d, J = 8.4, 2H); 7.64 - 7.62 (m, 1H); 7.57 (t, J = 7.9, 1H); 7.46 (d, J = 8.2, 2H); 4.24 (quintett, J = 7.2, 1H); 3.58 (s, 3H); 3.04 - 2.98 (m, 2H); 2.60 - 2.51 (m, 2H); 1.24 (d, J = 7.3, 3H)

Analogously as described in example 11 but using appropriate starting material, compounds of formula I, wherein R_4 is as described in TABLE 3 below, having ^{1}H-NMR or m.p. as defined in TABLE 3 are obtained:

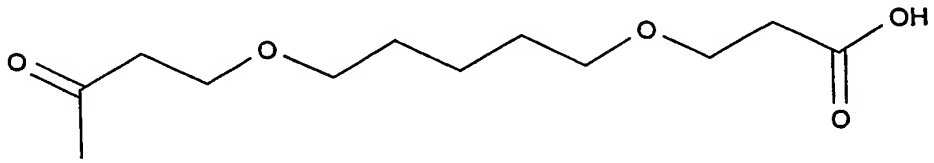
TABLE 3

Example	R_4	m.p./^{1}H-NMR (d_6-DMSO, 500 MHz, RT, unless given otherwisse)
12		12.61 (br.); 8.82 (d, J = 5.3, 1H); 8.09 - 8.06 (m, 3H); 8.01 (d, J = 5.2, 1H); 7.78 (d, J = 8.7, 2H); 7.63 - 7.61 (m, 1H); 7.58 - 7.54 (m, 1H); 7.45 (d, J = 8.3, 2H); 7.21-7.13 (m, 5H); 4.40 - 4.35 (m, 1H); 3.00 (dd, J = 13.9, 4.8, 1H); 2.79 (dd, J = 13.8, 9.7, 1H); 2.69 (t, J = 7.3, 2H); 2.12 - 2.08 (m, 2H); 1.79 (quintet, J = 7.3, 2H)

13		8.82 (d, J = 5.5, 1H); 8.13 - 8.12 (m, 1H); 8.11 - 8.09 (m, 1H); 8.00 (d, J = 5.2, 1 H); 7.79 (d, J = 8.2, 2H); 7.65 - 7.62 (m, 1H); 7.57 (t, J = 7.9, 1H); 7.46 (d, J = 8.2, 2H); 3.35 - 3.21 (m, 4H); 2.99 - 2.96 (m, 2H); 2.70 - 2.67 (m, 2H); 1.09 (t, J = 7.0, 3H); 0.98 (t, J = 7.0, 3H)
14		8.82 (d, J = 5.3, 1H); 8.12 - 8.07 (m, 2H); 8.00 (d, J = 5.3, 1H); 7.83 (t, J = 5.6, 1H); 7.78 (d, J = 8.8, 2H); 7.63 (m, 1H); 7.56 (t, J = 7.8, 1H); 7.45 (d, J = 8.6, 2H); 3.04 - 2.96 (m, 4H); 2.45 (m); 2.17 (t, J = 7.2, 2H); 2.07 (s, 6H); 1.47 (quintett, J = 7.1, 2H)
15		(400 MHz): 8.82 (d, J = 5.3, 1H); 8.31 (d, J = 7.7, 1H); 8.11 - 8.08 (m, 2H); 8.01 (d, J = 5.3, 1H); 7.77 (d, J = 8.7, 2H); 7.64 - 7.61 (m, 1H); 7.56 (t, J = 7.7, 1H); 7.44 (d, J = 8.2, 2H); 4.28 - 4.23 (m, 1H); 3.58 (s, 3H); 2.97 (m, 2H); 2.62 - 2.48 (m); 2.25 (t, J = 7.5, 2H); 1.90 (m, 1H); 1.75 (m, 1H)
16		12.64 (br); 8.82 (d, J = 5.2, 1H); 8.21 (d, J = 8.0, 1H); 8.11 - 8.07 (m, 2H); 8.01 (d, J = 5.3, 1H); 7.77 (d, J = 8.5, 2H); 7.64 - 7.61 (m, 1H); 7.56 (t, J = 7.9, 1H); 7.45 (d, J = 8.3, 2H); 7.22 - 7.11 (m, 5 H); 4.40 (dt, 1H); 3.01 (dd, J = 13.8, 5.1, 1H); 2.92 - 2.88 (m, 2H); 2.83 (dd, J = 13.7, 9.1, 1H); 2.55 - 2.43 (m)
17		8.83 (d, J = 5.3, 1H); 8.30 (d, J = 7.5, 1H); 8.12 - 8.08 (m, 2H); 8.01 (d, J = 5.3, 1H); 7.78 (d, J = 8.9, 2H); 7.64 - 7.62(m, 1H); 7.57 (t, J = 7.9, 1H); 7.45 (d, J = 8.4, 2H); 4.27 (dt, J = 5.3, 8.3, 1H); 3.59 (s, 3H); 3.55 (s, 3H); 3.04 - 2.96 (m, 2H); 2.62 - 2.49 (m, 2H); 2.38 - 2.31 (m, 2H); 1.99 - 1.92 (m, 1H); 1.83 - 1.76 (m, 1H)
18		8.83 (d, J = 5.2, 1H); 8.19 (d, J = 7.5, 1H); 8.11 - 8.07 (m, 2H); 8.02 (d, J = 5.3, 1H); 7.78 (d, J = 8.6, 2H); 7.64 - 7.62(m, 1H); 7.57 (t, J = 7.8, 1H); 7.47 (d, J = 8.1, 2H); 4.22 - 4.18 (m, 1H); 3.55 (two singlets, 6H); 2.78 (t, J = 7.4, 2H); 2.30 (t, J = 7.8, 2H); 2.18 (t, J = 7.2, 2H); 1.96 - 1.84 (m, 3H); 1.80 - 1.72 (m, 1H)

19		8.83 (d, J = 5.2, 1H); 8.10 -8.07 (m, 2H); 8.05 (d, J = 7.6, 1H); 8.01 (d, J = 5.2, 1H); 7.78 (d, J = 8.9, 2H); 7.63 - 7.61 (m, 1H); 7.57 (t, J = 7.9, 1H); 7.47 (d, J = 8.5, 2H); 4.15 (dt, J = 5.0, 8.4, 1H); 3.54 (s, 3H); 2.78 (m, 2H); 2.30 - 2.27 (m, 2H); 2.18 (t, J = 7.3, 2H); 1.96 - 1.90 (m, 1H); 1.88 - 1.82 (m, 2H); 1.78 - 1.70 (m, 1H)
20		8.83 (d, J = 5.5, 1H); 8.20 (d, J = 7.0, 1H); 8.11 - 8.08 (m, 2H); 8.02 (d, J = 5.2, 1H); 7.78 (d, J = 8.2, 2H); 7.65 - 7.62 (m, 1H); 7.57 (t, J = 7.9, 1H); 7.47 (d, J = 7.9, 2H); 4.21 - 4.15 (m, 1H); 3.54 (s, 3H); 2.78 (t, J = 7.5, 2H); 2.16 (t, J = 7.3, 2H); 1.89 - 1.82 (m, 2H); 1.18 (d, J = 7.3, 3H)
21		8.78 (d, J = 5.3, 1H); 8.15 (d, J = 7.3, 1H); 8.09 - 8.07 (m, 2H); 7.97 (d, J = 5.3, 1H); 7.84 (d, J = 8.3, 2H); 7.65 - 7.62 (m, 1H); 7.58 - 7.55 (m, 1H); 7.52 (d, J = 8.3, 2H); 4.90 (s, 2H); 4.35 - 4.28 (m, 1H); 4.02 (s, 2H); 3.58 (s, 3H); 1.25 (d, J = 7.3, 3H)

Example 22:

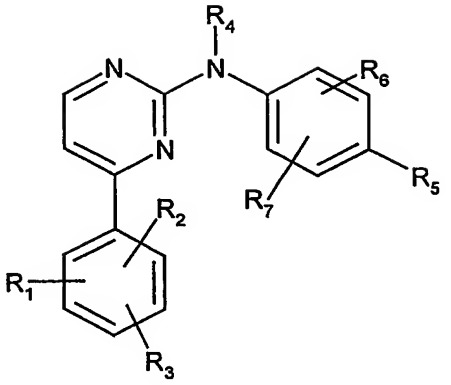
R_4 is 

A solution 6.5 g of 3-[5-(2-Chlorocarbonyl-ethoxy)-pentyloxy]-propionyl chloride in 10 ml dichloromethane is added dropwise to a mixture of 1 g of N-[4-(3-chloro-phenyl)-pyrimidin-2-yl]-N-(4-trifluoromethyl-phenyl)-amine, 10 mg of dimethylaminopyridine and 2.7 ml of diisopropyl ethylamine in dichloromethane. The mixture is stirred at RT, cooled and acetonitrile and water are added; the mixture is stirred further. The mixture is extracted with ethylacetate. The organic phase is washed, dried, solvent is stripped off and the product is obtained.

(d_6-DMSO, 500 MHz, rt): 8.83 (d, J = 5.2, 1H); 8.12 (t, J = 1.9, 1H); 8.10 (dt, J = 7.6, 1.5, 1H); 8.02 (d, J = 5.4, 1H); 7.79 (d, J = 8.3, 2H); 7.64 (m, 1H); 7.57 (t, J = 7.9, 1H); 7.44 (d, J = 8.1, 2H); 3.68 (t, J = 6.4, 2H); 3.51 (t, J = 6.4, 2H); 3.03 (t, J = 6.5, 2H); 2.39 (t, J = 6.3, 2H); 1.47 - 1.39 (m, 4H); 1.28 - 1.21 (m, 2H)

Patent Claims

1. A compound of formula



I

wherein

at least one of R_1, R_2 and R_3 is halogen or haloalkyl, and the other of R_1, R_2 and/or R_3 are independently of each other hydrogen, halogen or haloalkyl,

R_5 is halogen or haloalkyl,

R_6 and R_7 independently of each other are hydrogen, halogen, or haloalkyl, and

R_4 is hydrogen, alkyl or a group of formula

$-CO-(CH_2)_n-CO-R_8$,

$-CO-(CH_2)_n-O-(CH_2)_n-CO-R_8$ or

$-CO-(CH_2)_n-O-(CH_2)_m-O-(CH_2)_n-R_{12}$, wherein

R_8 is $-OR_9$, $-NR_{10}R_{11}$, an amino acid or an ester thereof bound via the amino group,

R_9 is hydrogen or alkyl,

R_{10} and R_{11} independently of each other are H, alkyl or substituted or unsubstituted aminoalkyl;

R_{12} is hydrogen, alkyl, carboxyl or carboxylic ester,

n is 0 to 4, and m is 1 to 5.

2. A compound of claim 1 wherein one of R_1, R_2 or R_3 is chloro and the other two are H, one of R_5, R_6 or R_7 is trifluoromethyl and the other two are hydrogen, and

R_4 is $-CO-(CH_2)_nCO-R_8$, wherein

R_8 is OR_9, $N(CH_3)_2$, $N(CH_3CH_2)_2$, $NH-(CH_2)_3-N(CH_3)_2$, amino acid or an ester thereof, preferably an amino acid selected from the group consisting of alanine, phenylalanine, glutamic acid and lysine, wherein the binding is effected via the α- amino group or in the case of e.g. lysine via the ε-amino group,

R_9 is hydrogen or alkyl, and n = 1 to 4, preferably 2,3 or 4.

3. A compound of claim 1 wherein one of R_1, R_2 or R_3 is chloro and the other two are H, one of R_5, R_6 or R_7 is trifluoromethyl and the other two are hydrogen, and R_4 is-CO-$(CH_2)_n$O-$(CH_2)_n$-CO-R_8 wherein R_8 is OR_9, R_9 is hydrogen or alkyl, and n is 1 to 4, preferably 2, 3 or 4.

4. A compound of claim 1 wherein one of R_1, R_2 or R_3 is chloro and the other two are H, one of R_5, R_6 or R_7 is trifluoromethyl and the other two are hydrogen, and R_4 is –CO-$(CH_2)_n$-O-$(CH_2)_m$-O-$(CH_2)_n$-R_{12} wherein R_{12} is hydrogen, alkyl, carboxyl or carboxylic ester, n is 1 to 4, preferably 1 or 2, and m is 1 to 5, preferably 2 or 5.

5. Use of a compound of any one of claims 1 to 4 in the preparation of a medicament for the therapy of IgE-mediated diseases, e.g. of diseases mediated by IgE expression.

6. A method of treatment of IgE-mediated diseases which comprises administering a therapeutically effective amount of a compound of any one of claims 1 to 4 to a subject in need of such treatment.

7. A compound of any one of claims 1 to 4 for use as a pharmaceutical.

8. A pharmaceutical composition comprising a compound of any one of claims 1 to 4 in association with at least one pharmaceutical carrier or diluent.

9. Use of an amine, which is substituted by
- phenyl-substituted pyrimidin; and
- phenyl; and
- a third substituent, e.g. R_4 as defined in claim 1 to 4,
in the preparation of a medicament for the treatment of IgE-synthesis-mediated diseases.

IL/19-Sep-2002

Abstract

Use of an amine, which is substituted as described in the preparation of a medicament for the treatment of IgE-synthesis-mediated diseases.

IL/19-Sep-2002